PHARMACOLOGY

Comm.
Dr. Gardner
Dr. Meier
Dr. Sommers

THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application for Research Grant
(Use extra pages as needed)

Date: 5/7/73

RECEIVED
MAY 9 1973

1. Principal Investigator (give title and degrees):

John A. Rosecrans, Ph.D.
Associate Professor
Dept. of Pharmacology

2. Institution & address:

Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

3. Department(s) where research will be done or collaboration provided:

Department of Pharmacology

4. Short title of study:

State Dependent Properties of Nicotine Related Compounds

5. Proposed starting date:
1-1-74
6. Estimated time to complete:
3 yrs
7. Brief description of specific research aims:

The major objective of this research will be to study the behavioral effects of various analogs and metabolites of nicotine, or compounds believed to have behavioral effects similar to nicotine. We hope to study these various compounds from the following points of view:

1. Specific behavioral effects of each compound to be studied.
2. The ability of such compounds to block nicotine's behavioral effect.
3. To test the ability of such drugs to act like nicotine, that is transfer to the nicotine state.

It is hoped that this study will allow us to establish the means by which we will be able to detect compounds suspected of having nicotine-like behavioral effects.

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8. Brief statement of working hypothesis:

Research conducted in this laboratory (1-8) has shown that learning a specific task can be made contingent upon the drug state an animal is in. Thus, in such situations a rat must be able to detect the drug state it is in in order to obtain a positive or negative reinforcement in a choice situation. The drug, in this situation is acting as a discriminative cue. Another application of this approach involves studying learning in the drug state. This specific approach involves studying how animals learn various tasks in the drug state and then testing their performance rate in the non-drug state. Generally, drugs with powerful behavioral effects produce what is called dissociative learning, i.e. the behavioral performance of a task learned in the drug state will be less than when tested in the non-drug state. Both approaches provide us with the same general information and are considered to be a function of state dependent behavior.

What has been done in this laboratory has been to use this StD paradign to determine how nicotine is producing its behavioral effects. From this approach, we have found the following: a) the state dependent effect is the result of central cholinergic stimulation, b) nicotine is acting on a specific receptor seperate from muscarinic sites, c) brain norepinephrine systems appear to be involved and d) the state dependent effect appears to follow the classical pharmacological mechanisms which depend upon the drug levels at some central site. Essentially, the task we used asked the animal whether it perceived a drug response. In other words, the animal, by the responses it made indicated whether it had perceived nicotine or not. Thus, we have been able to study the drug effect by challenging these responses through various other agents

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which would either block nicotinic or muscirinic receptors in the CNS, or would inhibit specific enzyme systems involved with the control of specific biogenic amine systems.

Aside from using these techniques to study mechanisms by which nicotine may be producing its behavioral effects, an attempt was also made to determine the specificity of this drug effect. In other words, we attempted to determine what drugs if any, could produce a nicotine cue. Interestingly, nicotine did not transfer to any of the drugs studied. Drugs such as d-amphetamine, arecoline and LSD and lobeline were studied in this regard. The rational for the current study will be based upon the above ideas that drugs producing similar behavioral effects will transfer, or generalize, to each other. This has been shown amongst several drugs such as halucinogenic drugs. In rats trained to discriminate between LSD and saline, mescaline was interperted or perceived by these animals as producing effects similar to LSD. On the other hand, LSD would not transfer to a drug such as d-amphetamine. Rats given d-amphetamine responded as if they perceived, or had been given saline.

In view of this, we hope to ask the following questions concerning analogs and metabolites of nicotine:

1. Does a compound similar in structure to nicotine, or a metabolite of nicotine, have state dependent effects of its own?

2. Can the nicotine state transfer to the compound in question? More specifically, will an animal trained to discriminate between nicotine and non-drug states perceive such compounds as producing effects similar to nicotine.

9. Details of experimental design and procedures (append extra pages as necessary)

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1. Compounds to be tested

At present, we intend to study drugs related to nicotine in structure or behavior such as lobeline, cotinine, nicotinemethyliodide (a peripheral nicotine-like drug) and nornicotine. The above compounds were chosen because of their ready availability, and the fact that they might be the best ones to test such a screening procedure. While lobeline has been found to have no nicotine-like effect in this laboratory, this drug has not been completely studied. Furthermore, we would also like to study it in greater detail from the point of view of having effects of its own. In other words, instead of trying to determine whether the nicotine state will transfer to such compounds as a primary objective, we would also like to study each compound in terms of it's own possible state dependent effect. This is of extreme importance in terms of attempting to find out what compounds in tobacco have behavioral effects of their own.

2. Overall Behavioral Approach

Compounds will be studied in Aprague Dawley male rats and male mice in various phases. These phases will include the following: (1) initial screening studies will be carried out in both passive and active avoidance proced procedures, 2) Analagous studies will be conducted in a similar population of rats, 3) Compounds having state dependent effects of their own [determined from 1) and 2)] will be studied in operant procedures involving rats [this will be accomplished by, a) determining whether the nicotine cue will transfer to such compounds, b) or whether rats can be trained to discriminate between the drug and non drug state], and 4) compounds will also be studied as antagonists in rats trained to discriminate between nicotine and saline. In these latter approaches a population of trained rats will be maintained to test a compound as to whether it has nicotine-like or antagonist properties. This will be an ongoing experiment and will involve several well trained animals.

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3. Specific techniques

A. Passive Avoidance Studies in Mice and Rats

In this procedure an animal is placed in an unfamilar environment which is bright, and the time to enter a safer darkened area determined. In the case of rats, each is placed in a circular open field (diameter equal to 24 inches) with a bright light suspended 18 inches over the area. Usually a rat will enter into the adjacent dark cage through an opening within 30 seconds. Once the animal has entered the safe area, a guillotine door is closed and the animal presented two one second shocks over a one minute period. Twenty-four hours later, these animals will be returned to the open field and the time for entering the cage shocked in 24 hours previously determined. Generally, rats presented the shock prior, will not enter the cage easily. Because of this, a 300 second maximum exposure time is utilized. The average time or latency for entering is about 220 seconds. With mice the apparatus used is smaller, and the cut off latency on the testing day is 600 seconds. In the experimental design a 2 x 2 drug saline paradign is utilized. That is, rats are trained and tested under all conditions. (Table presented below).

Group	Trained	Tested
A	Nicotine	Saline
B	Nicotine	Nicotine
C	Saline	Nicotine
D	Saline	Nicotine

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In this approach rats trained under nicotine will enter the shock chamber faster when tested in the non-drug state (group A) than when tested in the drug state (Group B). On the other hand, rats trained under saline will retain the passive avoidance response regardless of drug treatment of the test state. (Groups C & D)

This response has been studied with nicotine and has been observed to produce a classical dissociation of learning or state dependent effect. Under such a test, any drug having a power C.N.S. effect will produce this type of behavior. It is possible that some drugs will produce an symetrical association, that is, the drug effect would block avoidance in both groups A and C. This would suggest that the drug may also be affecting memory, which would also indicate a powerful CNS effect, and would suggest that such a compound should be studied in greater detail. Of special importance is the fact that this technique will detect C.N.S. drug effects at dosage levels lower than that usually observed in conditioned avoidance behavior, or spontaneous activity experiments.

B. Active Avoidance Studies in Rats and Mice

Another approach to be used in this study, will involve the same general model as described above. In this situation, a rat will be trained to avoid a shock (one way or two shuttle box) in the drug state and performance studied in drug and non-drug states. The design will be similar to the 2 x 2 design described above in the passive avoidance test. The data obtained should be similar, that is if a drug has a strong state dependent effect, then performance of the task learned in the drug state will be lower when tested in the non-drug state. Both avoidance (passive and active) procedures will provide similar types of information. However, at this time it is felt that both procedures will be extremely important in attempting to obtain a complete picture of each drug studied.

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Especially since it is a very real possibility that drugs affecting or having state dependent effects in one procedure will not on the other hand.

C. Training Rats to Discriminate Between Nicotine and Non-Nicotine States

Rats will be trained to discriminate between nicotine and non-nicotine states using a standard two-lever operant chamber. In this schedule animals will be food deprived and initially shaped to press both levers for a food reinforcement. Once training has been completed rats will then be trained to press one lever under the nicotine state and the other lever under the saline state. The schedule of reinforcement will involve a ratio schedule. Most likely, we will be using an FR 5-10. Thus an animal to obtain a food reinforcement, must press the lever 5-10 times for reinforcement. In the initial training procedure, rats will be given nicotine or saline, placed in the operant chamber 5-10 minutes after s.c. injection, and trained on the appropriate lever under each drug state. Experimental sessions will last for 15 minutes; the first two and a half will not be reinforced to determine whether an animal is responding on the correct lever. In this study animals under nicotine will learn to press the correct lever 80-90% of the time which will be our measure of learning. Data is calculated as a percentage of the levers responses on the correct or nicotine lever divided by total responding on both levers. Once training has reached maximum, drugs will be studied as to their ability to generalize to the nicotine state. Learning under the nicotine state is usually defined as rats who will respond on the nicotine correct lever 90% of the time when given nicotine or who respond 30% of the time on the lever when given saline. Thus, a discrimination index or some difference between the two states averages 50-60%.

Once animals have reached training criteria, experimental compounds will be tested on one or two sessions every week. In this situation, drugs

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will be administered, and animals then given a two and a half minute non-reinforced session. These animals will not be given a total 15 min. presentation and will not be reinforced. Under these circumstances drugs having nicotine-like properties will produce an effect in these animals such that animals will press the nicotine correct lever. In this procedure, several doses of each compound can be tested within one month. Doses to be studied in this study will be either equimoler to nicotine, or doses suspected of having CNS effects. CNS effects will also be determined in preliminary studies of each compound, or from data extrapilated from research conducted by other investigators.

Drug antagonism studies can be conducted in the same group of animals. Care will be taken to spread out these studies so that they will not interfere with drug transfer research. It might be useful to use a different population of animals to study either transference or antagonism effects of various drugs. In such studies, dose-response experiments will be conducted in which drugs will be given at a specified time interval before a dosage of nicotine. In general, antagonism studies will be conducted 15 to 30 minutes before a dose of nicotine is administered. Thus, animals will be injected with the suspected compound and then administered nicotine 30 minutes thereafter. Ten minutes after this, the animal will be placed in the operant chamber and given one test session. That is, animals will be given two and one half minutes in the operant chamber, but not given any reinforcement. A drug which will produce an antagonistic effect will block the effects of nicotine such that the animals will respond as if they were given saline, and will press the saline correct lever. In this type of investigation, two types of studies can be conducted in which 1) a dose response of the antagonist drug can be studied as blocking the effects of nicotine or 2) nicotine can be studied in a dose response fashion in an

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attempt to overcome the effects of the antagonist. Thus, aside from studying the general antagonist effects of such drugs, drug competition can also be evaluated in such studies.

D. Studies Involving the Discriminative Properties of Drugs to be Evaluated In This Project

Besides studying the effects of experimental drugs in the passive and active avoidance studies indicated above, we would also like to determine if any active CNS drug has discriminative cue properties of its own. These studies will be conducted in the same manner as the procedures described above for studying nicotine as a discriminative cue (C). Dose regimens will be determined by previous studies. Such studies will be conducted in the same manner as above, and will be conducted for a period of 5 to 8 weeks. It is felt that animals which do not learn to discriminate between such a compound and non-drug states in that period of time does not have sufficient state dependent effects to study any further. If a compound still appears to be interesting from an experimental point of view based on other studies conducted in parts A-D, then we will make a more intensive evaluation of the state dependent properties of the drug.

If a compound can be shown to act as a discriminative stimulus or cue, then a more complete psychopharmacological investigation of this drug will be conducted. The types of studies to be conducted under this condition will involve dose response, and time duration experiments. Compounds having such discriminative properties will also be studied from the point of view of mechanism of action. Thus, these compounds will be studied to determine if they stimulate muscarinic cholinergic receptors. An appropriate blocking drug, such as atropine and mecamylamine will be utilized for this purpose. If such compounds have specific qualities resembling cholinergic properties of nicotine, we will also expand thest studies to include in evaluation of

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what other systems these drugs might be effecting. Thus, enzyme inhibitors will be inhibitors will be utilized which will inhibit either brain norepinephrine or brain 5-hydroxytryptamine systems.

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3. Schechter, M. D., and J. A. Rosecrans: Behavioral tolerance to an effect of nicotine in the rat. Arch. Int. Pharmacodyn. 194, 134 (1971).

4. Schechter, M. D., and J. A. Rosecrans: Nicotine as a discriminative stimulus in rats depleted of Norepinephrine or 5-hydroxytryptamine. Psychopharmacologia 24, 417 (1972).

5. Schechter, M. D., and J. A. Rosecrans: Effect of mecamylamine on discrimination between nicotine - and arecoline - produced cues. European J. Pharmacol. 17, 179 (1972).

6. Schechter, M. D., and J. A. Rosecrans: Lysergic acid diethylamide (LSD) as a discriminative cue: drugs with similar stimulus properties. Psychopharmacologia 26, 313 (1972).

7. Schechter, M. D., and J. A. Rosecrans: Nicotine as a discriminative cue in rats: inability of related drugs to produce a nicotine - like cueing effect. Psychopharmacologia (In press).

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

We have three laboratories available for this research. These laboratories are equipped with behavioral and chemical instrumentation sufficient to conduct any aspect of the research described herein. However, if this grant was awarded, additional behavioral equipment would be needed to take of the increased research load.

11. Additional facilities required:

None Needed

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12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available):

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R: REDACTED MATERIAL

14. First year budget

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
John A. Rosecrans, Ph.D.	25	
Technical		
"Behavioral Technicians to be recruited"	100	REDACTED
Sub-Total for A		REDACTED
B Consumable supplies (by major categories)		
Research animals:		
2000 rats		3000
4000 mice		1200
Sub-Total for B		4200
C Other expenses (itemize)		
Fringe Benefits - 10% of		700
Office supplies publication Costs etc.		200
Travel to Scientific meetings		300
Sub-Total for C		1200
Running Total of A + B + C		REDACTED
D Permanent equipment (itemize)		
Additional Behavioral Equipment: This will include two operant chambers and an automated one way-shuttle box (Leigh Valley Electronics, Inc. and Lafayette Instrument Co.)		
Sub-Total for D		5000
E. Indirect costs (16% of A+B+C)	E	1860
15. Estimated future requirements	Total request	20260

	Salaries	Consumable Supp	Other Expenses	Permanent Equip.	Ind'rect Costs	Total
Year 2	REDACTED	4200	940		1891	REDACTED
Year 3		4200	980		1947	

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Investigation of the importance of central biogenic amines on the behavioral effects of nicotine	A.M.A.E.R.F.	$88,520	2/1/73 - 1/31/76

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Effects of acute and chronic methadone treatment on Psychological and endocrine parameters in animals	N.A.D. MH-22261-01	$160,959	9/1/72-8/31/75

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made"

Principal investigator

Typed Name Dr. John A. Rosecrans

Signature John A. Rosecrans Date 4/30/73

Telephone 703 (Area Code) 770-4691 (Number) none (Extension)

Checks payable to:

c. Walter P. Lossing
Comptroller-Treasurer
Mailing address for checks

Virginia Commonwealth University
Medical College of Virginia
1200 East Broad Street
Richmond, Va. 23298

Responsible officer of institution

Typed Name Dr. M. Pinson Neal, Jr.

Title Provost VCU/MCV

Signature [signature] Date 5/2/73

Telephone 703 (Area Code) 770-5150 (Number) (Extension)

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CURRICULUM VITAE

John Adam Rosecrans

Personal

REDACTED

Education

Primary: Public School Systems of Jamaica, Brooklyn, and Long Beach, N.Y.
Secondary: Long Beach Junior and Senior High School, N.Y.
College: B.S. In Pharmacy, St. John's University of New York.
Graduate School: M.S. (Pharmacology), 1960, University of Rhode Island, Kingston, Rhode Island
Ph.D. (Pharmacology), 1963, University of Rhode Island, Kingston, Rhode Island.

Professional Experience

Instructor in Pharmacology (September 1960 - June 1961), College of Pharmacy, University of Rhode Island, Kingston, Rhode Island.

Research Assistant Professor (August 1964 - November 1965), School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania.

Part-time Instructor in Chemistry (September 1966 - July 1967), New Haven College, New Haven, Connecticut.

Assistant Professor (July 1967 - July 1970), Department of Pharmacology, Medical College of Virginia, Richmond, Virginia.

Associate Professor (July 1970 - Present), Department of Pharmacology, Medical College of Virginia, Richmond, Virginia.

Professional Societies

REDACTED

REDACTED

Awards and Fellowships

The Phi Sigma and Sigma Xi awards at the University of Rhode Island for graduate work leading to the M.S. degree in Pharmacology.

U.S.P.H.S. Predoctoral Research Fellowship (N.I.M.H.), University of Rhode Island (June 1961 - February 1963), Sponsor - Dr. John J. DeFeo.

U.S.P.H.S. Postdoctoral Research Fellowship (N.I.M.H.), University of Michigan (February 1963 - August 1964), Sponsor - Dr. Edward F. Domino.

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Awards and Fellowships (continued)

Postdoctoral Trainee in Psychiatry, Yale University (November 1965 - July 1967), Sponsor - Dr. Daniel X. Freedman and Dr. Roger K. McDonald.

Research Interests

Biochemical and Psycho-pharmacology with special interests in correlations between biochemical, electrophysiological and behavioral events associated with CNS acting drugs.

Research Grants

Research conducted by Dr. John A. Rosecrans has been largely supported by the AMA-ERF Committee on Tobacco and Health. Dr. Rosecrans has also had some support from the NIMH and has one grant approved, but not yet funded.

Journal Activities

Dr. Rosecrans is Regional Editor for the journal, Pharmacology, Biochemistry and Behavior.

Educational Activities at the Medical College of Virginia

Professional: involved in teaching CNS Pharmacology at MCV; including Schools of Pharmacy, Medicine, and Dentistry.

Graduate: has presented courses in psychopharmacology involving graduate students in Pharmacology and Psychology. Dr. Rosecrans is also currently involved in a collaborative course on drug dependence with the Department of Sociology. He is also on the graduate committee for several students in Psychology and has two students working toward Ph.D. degrees in Pharmacology.

Undergraduate Education: has been involved in presenting a pharmacology course to undergraduate students at Virginia Commonwealth University during the last three years. Dr. Rosecrans has been coordinator of this program during this period. He has also introduced a new undergraduate course on drug dependence. This latter program has also enabled several sociology and psychology majors to conduct independent projects in pharmacology.

Community Education: Dr. Rosecrans was coordinator of a teacher-training program involving 250 students. This was in conjunction with the Council on Drug Abuse Control in Richmond and was supported by LEAA.

Adult Education: Dr. Rosecrans has been involved with the education of adults via the extension division of Virginia Commonwealth University. Three 10-hour classes have thus far been presented.

Additional Activities: Dr. Rosecrans has been involved in two additional programs. The first involves a medical elective to assist students in learning about drug abuse problems. In the second program, a summer study program was established in which three pharmacy students studied in the area of drug abuse. In this program students work part-time at the Medical

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Educational Activities at MCV - Additional Activities (continued)

College of Virginia Methadone Clinic, conduct independent research projects, and participate in a weekly seminar series. These students are in the second summer of the program.

University Committees

Dr. Rosecrans is a member of the following committees: Student Evaluation of Faculty (Graduate School), Research Advisory Committee (Graduate School), and Drug Education Curriculum Committee (Universities).

Abstracts of Papers Presented at Scientific Meetings

Rosecrans, J.A., H.W. Youngken, Jr. and J.J. DeFeo: A pharmacological investigation of Valerian officianlis, Linne. A.Ph.A. Convention, Washington, D.C., 1960.

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Weiss, G.B. and J.A. Rosecrans: Alteration of Serotonin-C^{14} uptake and metabolism in intestinal smooth muscle. Pharmacologist 11: 267, 1969.

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Rosecrans, J.A., N. Watzman and J.P. Buckley: The production of hypertension in amle albino rats subjected to experimental stress. Biochem. Pharmacol. 14, 1707, 1966.

Guarino, A.M., J.A. Rosecrans, A. Mandello and J.J. DeFeo: Effects of isolation on the biochemical effects of the monamine oxidase inhibitor, MO-911. Biochem. Pharmacol., 16: 227, 1967.

Aghajanian, G.K., J.A. Rosecrans, and M.H. Sheard: Serotonin release in the forebrain by stimulation of the midbrain raphe. Science 15: 402, 1967.

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